Guidelines for future research in constraint-induced movement therapy for children with unilateral cerebral palsy: an expert consensus

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ABBREVIATIONS

AHA	Assisting Hand Assessment
CCT	Controlled clinical trial
CIMT	Constraint-induced movement therapy
EUnetHTA	European network for Health Technology Assessment
MAS	Modified Ashworth Scale
mCIMT	Modified constraint-induced movement therapy
PMAL	Pediatric Motor Activity Log
QUEST	Quality of Upper Extremity Skills Test
RCT	Randomized controlled trial
SDD	Smallest detectable difference

AIM The aim of this study was to provide an overview of what is known about constraint-induced movement therapy (CIMT) in children with unilateral cerebral palsy (CP), to identify current knowledge gaps, and to provide suggestions for future research.
METHOD Nine experts participated in a consensus meeting. A comprehensive literature search was conducted and data were summarized before the meeting. The core model produced by the European network for Health Technology Assessment was used as a framework for discussion and to identify critical issues for future research.
RESULTS All models of CIMT have demonstrated improvements in the upper limb abilities of children with unilateral CP. A consensus was reached on 11 important questions to be further explored in future studies. The areas of highest priority included the effect of dosage, the effect of repeated CIMT, and the impact of predictive factors, such as age, on the response to CIMT. Consensus suggestions for future study designs and the use of validated outcome measures were also provided.
INTERPRETATION The CIMT construct is complex, and much remains unknown. It is unclear whether a specific model of CIMT demonstrates superiority over others and whether dosage of training matters. Future research should build upon existing knowledge and aim to provide information that will help implement CIMT in various countries with different health care resources and organizational structures.

Over the past decade, interest in constraint-induced movement therapy (CIMT) for children with unilateral cerebral palsy (CP) has increased dramatically. The number of publications has grown in this period from a few single case studies to over 70 studies. However, unlike areas of medical research that follow a progressive staging of studies to build on existing knowledge, the development of CIMT research has been haphazard, consisting of a range of diverse, often small, trials that rarely build upon each other. The variation in the content and intensity of CIMT intervention, as well as the different study designs, make it extremely difficult to draw conclusions about what the key aspects of CIMT are and for a comparison of effect to be made between different CIMT protocols. Importantly, this limits confidence in choosing a model of CIMT to implement in clinical practice. The wide range of outcome measures used and short duration of follow-up also diminishes the ability to draw conclusions on clinically important, real-life effectiveness. Therefore, it is essential to explore what is currently known about CIMT and identify the current knowledge gaps that need to be addressed in order to advance this area of paediatric rehabilitation.

Aims and framework for development of expert consensus

In January 2012, a group of nine international experts attended a consensus meeting in Stockholm, Sweden, with the aim of developing clear recommendations for guiding future research for CIMT in children with unilateral CP. A consensus process based on a literature search, a valid framework to identify key questions of clinical effectiveness relating to CIMT, and a collaborative discussion among an

international expert group will serve as a useful guide for future research. As a result this paper aims to (1) identify the current knowledge gaps regarding CIMT in children with unilateral CP and (2) present prioritized suggestions for future research.

What this paper adds

- The CIMT construct remains complex and much is still unknown.
- Consensus agreement identified 11 questions to be explored in future studies.
- Future research should focus primarily on the effect of dosage, the effect of repeated treatment, and predictive factors such as age.

METHOD

Preparation of the consensus process

Before the consensus meeting, a literature search was performed (BH). Additionally, with the aim of identifying clinically relevant, unanswered questions related to CIMT, a survey was produced using the European network for Health Technology Assessment (EUnetHTA) and completed by all members of the consensus group (but IAR).[1]

Literature review

A comprehensive literature search was conducted to guide discussion based on the current available literature. Key search terms were 'cerebral palsy', 'hemiplegia', 'CI therapy', 'constraint-induced movement therapy', and 'forced use'. The databases that were searched included the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 3), MEDLINE (up to January, week 4, 2012), EMBASE (up to January 2012), CINAHL (up to January, week 4, 2012), and PsychInfo (up to January, week 4, 2012). In addition, reference lists of articles and conference abstracts were examined. All studies published in English, studying children with unilateral CP aged between 0 years and 19 years, and comparing the effect of any CIMT with a comparison treatment or no treatment were considered. Additionally, two randomized controlled trials (RCTs) submitted for publication by consensus group members (BH, KK) were considered. This search strategy identified 379 articles. Of these, 23 were RCTs or controlled clinical trials (CCTs) and 45 were single-group/case study or pretest/posttest designs. During the consensus meeting, we focused on RCTs and CCTs; however, content from other studies was considered during the consensus process when the identified knowledge gaps needed to be further explored.

Before the meeting, each expert was provided access to all the literature through a common database. They were expected to read all publications relating to RCTs and CCTs (see Table I), and three of these studies were specifically assigned to each expert to be read more carefully, guided by a list of areas to consider based on the work of Kunz et al.[2] A formal rating of methodological quality for each trial was not undertaken as the consensus process was aimed at identifying current knowledge gaps as opposed to conducting a systematic review or producing guidelines for clinical practice.[3–5]

European network for Health Technology Assessment (EUnetHTA)

To capture a broad perspective of the knowledge on CIMT, a survey of the EUnetHTA core model for interventions was completed by each member of the consensus group. The EUnetHTA project (2006) was developed to connect public health technology assessment agencies, research institutions, and health ministries in order to enhance exchange of information and to support policy decisions by the EU Member States.[1] The EUnetHTA project has produced a core model that can be used when deciding upon the implementation of a new intervention (www.eunethta.eu). The model provides elements and specific issues (e.g. questions) that have been identified as particularly significant for decision making including safety, effectiveness, cost, ethical, social, organizational, and legal aspects.

The generic survey consisted of a list of 110 issues. Each issue was rated for relevance regarding consensus discussion (1 = borderline, 2 = moderate, 3 = high) and the need for future CIMT research (1 = borderline, 2 = moderate, 3 = high). Fifty-seven issues were rated by at least six out of eight responders as being moderately or highly relevant for CIMT and requiring further research.

Consensus process for identifying current knowledge gaps

At the commencement of the consensus meeting, a summary of outcomes from all RCTs and CCTs was presented (BH). In addition, a summary of the EUnetHTA survey was provided, highlighting issues of high or moderate relevance for further discussion (IA-R). Thereafter, the consensus process identified current knowledge gaps. The specific content of questions to be further explored were prioritized based on (1) an evaluation of the context-specific importance of the various issues from the EUnetHTA core model and (2) a lack of knowledge, guided by the literature review. When questions were identified by the consensus group, the literature was specifically reviewed to summarize the existing evidence relating to these questions. Discussions continued until no further critical questions were identified. Thereafter, questions were merged into broader categories, resulting in 11 questions that required further exploration.

Considerations on the reporting and interpretation of treatment effects for CIMT and issues relating to the use of outcome measures were also addressed during the literature review and consensus process. These were viewed by the expert group as important for ensuring the quality of future research in CIMT. To strengthen future research, we reported on the strengths and limitations of some commonly used outcome measures and we reported challenges regarding interpretation of treatment effects across studies.

Table I: List of randomized or controlled clinical trials

Authors	Year	*n*	Mean age (y:m)	Title	Model classification	Comparison	Restraint type
Taub et al.[6]	2004	18	3:6	Efficacy of CIMT for children with CP with asymmetric motor impairment	Signature CIMT	Usual care	Cast
Charles et al.[7]	2006	22	7	Efficacy of a child-friendly form of CIMT in hemiplegic CP: a randomized control trial	mCIMT	Usual care	Sling
Sung et al.[8]	2005	31	3	Efficacy of forced-use therapy in hemiplegic CP	mCIMT	Usual care	Cast
Smania et al.[9]	2009	10	3:6	A mCIMT programme improves paretic arm use and function in children with CP	mCIMT	Usual care	Mitt
Taub et al.[10]	2011	20	4	Treatment of congenital hemiparesis with paediatric CIMT	Hybrid	Usual care	Cast
Eliasson et al.[11]	2011	25	2	An ecological approach of CIMT for 2- to 3-year-old children: a randomized control trial	mCIMT	Usual care	Mitt
Aarts et al.[12]	2010	52	5	Effectiveness of mCIMT in children with unilateral spastic CP: a randomized controlled trial	Hybrid	Usual care	Sling
Eliasson et al.[13]	2005	41	2:6	Effects of CIMT in young children with hemiplegic CP: an adapted model	mCIMT	Usual care	Mitt
Park et al.[14]	2009	32	NR	The short-term effects of combined mCIMT and botulinum toxin injection for children with spastic hemiplegic CP	mCIMT	Bimanual	Splint
de Brito Brandao et al.[16]	2010	16	6	Adapted version of CIMT promotes functioning in children with CP: a randomized controlled trial	Hybrid	Usual care	Bandage
Al-Oraibi et al.[17]	2011	22	5	Implementation of CIMT for young children with unilateral CP in Jordan: a home-based model	mCIMT	NDT	Mitt
Case-Smith et al.[18]	2011	18	4	Multicentre randomized controlled trial of paediatric CIMT: 6-month follow-up	Hybrid	Hybrid with different intensity	Cast
Gordon et al.[19]	2011	42	6	Bimanual training and CIMT in children with hemiplegic CP: a randomized trial	mCIMT	HABIT	Sling
Lin et al.[20]	2011	21	7	Effects of home-based CIMT versus dose-matched control intervention on functional outcomes and caregiver well-being in children with CP	mCIMT	Hybrid	Bandage
Rostami et al.[21]	2011	14	6	Effect of treatment environment on mCIMT results in children with spastic hemiplegic CP: a randomized controlled trial	mCIMT	mCIMT in different environment	Cast
Sakzewski et al.[22]	2011	63	10	Randomized trial of CIMT and bimanual training on activity outcomes for children with congenital hemiplegia	mCIMT	Bimanual	Mitt
Wallen et al.[23]	2011	50	4	mCIMT for children with hemiplegic CP: a randomized trial	mCIMT	Intensive occupational therapy	Mitt
Xu et al.[24]	2011	68	5	Efficacy of CIMT and electrical stimulation on hand function of children with hemiplegic CP: a controlled clinical trial	mCIMT	Occupational therapy/ CIMT+ FES	Splint
Hsin et al.[25]	2012	22	7	Efficacy of CIMT on functional performance and health-related quality of life for children with CP: a randomized controlled trial	mCIMT	Usual care	Mitt
Hoare et al.[26]	2013	34	3	Intensive therapy following upper limb botulinum toxin-A injection in young children with unilateral CP	mCIMT	Bimanual	Mitt
Klingels et al.[27]	2013	51	9	Randomized controlled trial of mCIMT with or without therapy guided sessions in children with unilateral CP	Hybrid	mCIMT without therapy guided session	Splint
Facchin et al.[28]	2011	105	3	Multisite trial comparing the efficacy of CIMT with that of bimanual intensive training in children with hemiplegic CP post-intervention results	mCIMT	Bimanual	Mitt
Gordon et al.[29]	2008	16	7	Both CIMT and bimanual training lead to improved performance of upper extremity function in children with hemiplegia	mCIMT	HABIT	Sling

CIMT, constraint-induced movement therapy; CP, cerebral palsy; mCIMT, modified constraint-induced movement therapy; NR, not reported; HABIT, hand arm bimanual intensive training.

Summary and prioritization process

Following the consensus meeting, discussions continued by email and Skype until final consensus was reached for each question. Drafts of a manuscript were continuously sent to the expert group for review and comment. Upon reaching a consensus agreement, and as a last stage, independent prioritization of the importance of each question was undertaken using an anonymous, web-based survey. Importance was graded using a 5-point scale, where 1 was least important and 5 was extremely important. The mean

values of the nine expert opinions are reported in Figure 1. Based on these ratings, adjustment of the 'consensus for future research' sections for each question was performed and the manuscript finalized.

Definition for constraint-induced movement therapy

The literature review identified significant complexity and confusion relating to the definition of CIMT. The definitions of CIMT concepts used by the consensus group are described below.

First described by Edward Taub in 1993,[30] the original, or signature, model of CIMT, has been significantly adapted for use in children with CP. Across 24 RCTs/CCTs, 23 studies have altered at least one variable, including the type and intensity of the restraint of the well-functioning hand, the type and dosage of structured training, and the treatment environment. These variables have all been modified to a different extent to suit local factors such as organizational, cultural, social, and financial conditions. More recently there have also been models that incorporate a bimanual component to training (either concomitantly or immediately after unimanual training; see hybrid models, Table I). These models were developed to improve outcomes of CIMT; however, adaptations contribute to the complexity of previous attempts to define models of CIMT in paediatrics and create difficulties in understanding the specific influence of each variable.[4]

In order to distinguish CIMT from other models of upper limb training, the consensus group proposed two key ingredients that define CIMT: (1) restraint of the well-functioning upper limb (irrespective of device/type) and (2) intensive structured training (irrespective of type). These key ingredients are found in all models of CIMT but have been manipulated to various degrees between studies.

For the purpose of this consensus discussion, specific model types have been categorized according to the definitions detailed below.

Signature constraint-induced movement therapy. Taub's original model was initially developed for adults with hemiparesis following stroke. This involves restraint of the well-functioning upper limb for 90% of waking hours for at least 2 weeks, while intensively training the involved upper limb for 3 hours or more per day.[30,31]

Modified constraint-induced movement therapy (mCIMT). The key ingredients (restraint and intensive training) are included but vary from the signature model. Variables include: the type of restraint of the well-functioning upper limb (sling, cast, mitt/glove); the type of structured training (shaping/repetition, motor learning); the programme duration (hours per day) and length (number of weeks); and the location, context, and provider of training (home/camp, individual/group, therapist/parent).

Hybrid CIMT. The key ingredients are included and bimanual training is added to different extents. This model significantly alters the unimanual construct of the method.

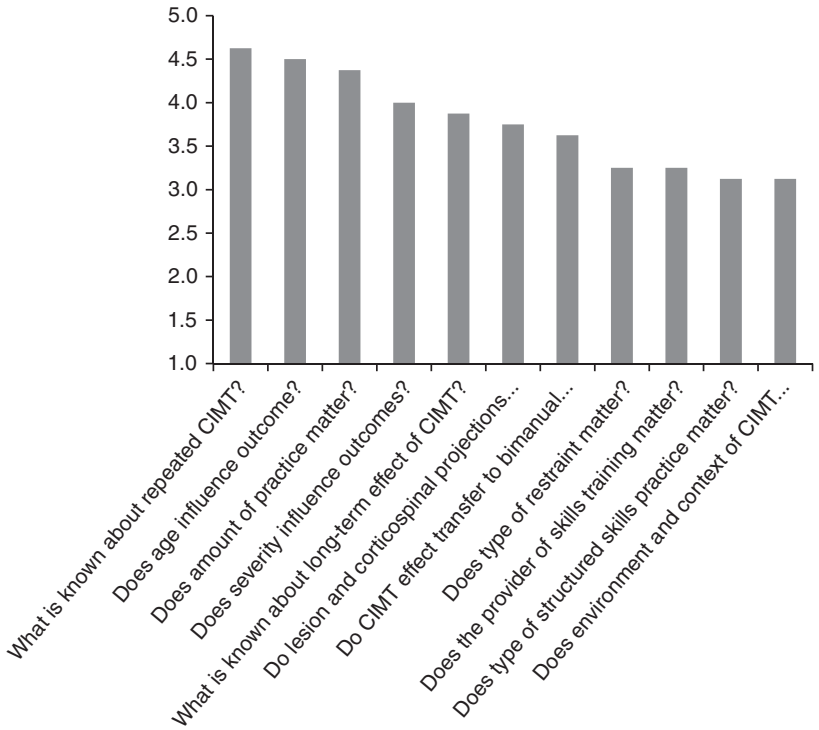

Figure 1: The importance of the defined questions on constraint-induced movement therapy (CIMT), showing the mean value of the nine experts opinions on a 1 to 5 grading scale, where 1 was of least importance and 5 was extremely important.

Forced use therapy. This involves restraint of the well-functioning upper limb but no specific structured training is provided. Forced use is related to, but not considered, CIMT.

Our approach. In this paper, CIMT is used as an umbrella term when discussing broader issues relating to the treatment including all variations of modified and hybrid CIMT. Where appropriate, the specific models defined above have been used. Since forced use therapy does not include structured training, these studies have been excluded from the umbrella term CIMT and will be specifically referred to as forced use.

RESULTS

The 11 questions are divided into three groups for future research, including (1) improving the current knowledge of the effectiveness of CIMT; (2) differences in variables and (3) optimal candidates for CIMT. Thereafter, results from the consensus discussion, with recommendations for future research, are provided.

Current knowledge on the effectiveness of CIMT

There is evidence from RCTs and CCTs that CIMT, irrespective of the model, is effective in improving the upper limb abilities of children with unilateral CP.[6–28,32] There is no evidence that a specific model of CIMT results in greater improvement than other models, and no study has directly compared different models. The broad variation in key ingredients across studies of CIMT precludes the ability to establish its effectiveness as a single, distinct intervention. The type of comparison/control group and the use of 48 different outcome measures makes comparison between studies difficult. Other factors, such as child characteristics, may also be influenced by outcomes since there is significant variation in individual response, as demonstrated by the large standard deviations within all studies. When CIMT is compared with alternative models of structured training, such as a bimanual approach, there are similar improvements in both treatments.[19,22,26,29]

Improving the current knowledge of the effectiveness of CIMT

What is known about long-term outcomes following CIMT?

Literature. Most studies report that improvements after CIMT are maintained at 3 or 6 months following intervention. Some studies have investigated longer term effects, with immediate post-treatment gains maintained at 12 months.[10,33–35]

Consensus for further research. A consistent follow-up period of 6 months following CIMT facilitates the comparison of outcomes between studies and is recommended. Follow-up effects are particularly important when investigating the effect of dosage (total amount of training performed) as different dosages could possibly yield the same initial effect but be differentially retained.[36] Longer-term follow-up is difficult with outcomes susceptible to influence from other treatments and on-going development. Therefore, long-term comparison between groups does not appear to be an optimal methodology. As an alternative, we recommend that a child's involvement in CIMT programmes should be documented and described in studies of longitudinal development of hand function.

What is known about the effect of repeated CIMT?

Literature. Knowledge of an additive effect from repeated CIMT is limited.[34,37,38] However, when specifically investigated, children were found to maintain improvements from the first programme of CIMT and make further gains after a second, with 1 year between programmes.[34]

Consensus for further research. Further studies investigating the repeated effects of CIMT are required. One option is to repeat the same design with 1-year intervals. This will allow exploration of the dose–response relationship and the age at which a ceiling effect may be reached. It is also important to understand how repeated programmes of CIMT are tolerated by children and their families by measuring the impact on adherence and participation in their social life.

Do the effects of CIMT transfer to improvements in bimanual performance and activities of daily life?

Literature. Outcomes from 11 trials using the Assisting Hand Assessment (AHA), a measure of the efficiency of the affected hand use in bimanual activities, have demonstrated clear evidence of the transfer of effect of CIMT to improvements in bimanual performance (see Table II). The transfer effect to daily activity performance has also been demonstrated using parent questionnaires,[12,16,17,26] goal attainment measures,[12,16,19,23,26] and measures of occupational performance.[12,21,23,26]

Consensus for further research. It is recommended that future studies of CIMT explore the amount of transfer to skills required for performance of daily activities for children with different ability levels.

Differences in variables of CIMT

Does type of restraint matter?

Literature. Across the studies, 19 RCTs/CCTs used removable devices such as a sling, mitt, splint, or glove while four used non-removable devices such as casting. The impact of the restraint may depend on the type of restraint as well as duration of restraint use. A non-removable cast typically results in a much greater intensity of unstructured training since it is worn at all times during the day. Removable restraints have predominantly been applied only during the structured training period. Currently, there are no studies directly comparing the effect of removable and non-removable restraints in combination with similar amounts of structured training. Compliance with different types of constraints has also rarely been investigated. In one study, parents reported that a fabric mitt, custom made for comfort and fit, was well tolerated.[39] In a specific investigation of tolerance of the type

Table II: Clinical outcome measures used in more than one of 24 randomized controlled trials, arranged in increasing order of use

Trial, first author	Year	2-Point discrimination	Caregiver Functional Use Survey	Peabody Developmental Motor Scales	Pediatric Evaluation of Disability Inventory (self-care)	ABILHAND-Kids	Active range of motion	Modified Tardieu Scale	Goal Attainment Scaling	Canadian Occupational Performance Measure	Bruininks-Oseretsky Test of Motor Proficiency	Grip strength	Melbourne Assessment of Unilateral Upper Limb Function	Quality of Upper Extremity Skills Test	Jebsen-Taylor Test of Hand Function	Modified Ashworth Scale	Pediatric Motor Activity Log	Assisting Hand Assessment
Taub et al.[6]	2004																X	
Sung et al.[8]	2005																	
Eliasson et al.[13]	2005																	X
Charles et al.[7]	2006	X	X								X	X			X	X		
Gordon et al.[29]	2008														X			X
Smania et al.[9]	2009																	
Park et al.[14]	2009							X								X	X	
Aarts et al.[12]	2010					X			X	X			X					X
de Brito Brandao et al.[16]	2010				X										X			
Al-Oraibi et al.[17]	2011																	X
Case-Smith et al.[18]	2011													X			X	X
Eliasson et al.[11]	2011																	X
Facchin et al.[28]	2011													X				
Gordon et al.[19]	2011								X					X	X			X
Lin et al.[20]	2011		X	X							X						X	
Rostami et al.[21]	2011										X						X	
Sakzewski et al.[22]	2011	X								X		X	X		X	X		X
Taub et al.[10]	2011						X									X	X	
Wallen et al.[23]	2011							X	X	X						X	X	X
Xu et al.[24]	2011			X			X					X				X		
Hsin et al.[25]	2012										X						X	
Hoare et al.[26]	2013				X			X	X	X				X		X		X
Klingels et al.[27]	2013					X	X					X	X		X	X		X
Sum		2	2	2	2	2	3	3	4	4	4	4	3	4	6	8	8	11

of restraint used (mitt, short and long splint), parents and children emphasized the importance of comfort with a long splint being least accepted.[40] Irrespective of restraint type, only a few adverse events have been reported.[10,18]

Consensus for further research. The potential for superior effects using non-removable casts compared with removable restraints needs to be investigated. While controlling for the amount of structured training, the type of restraint can be varied between groups (24h casting vs removable restraint only during structured skill training). This will specifically investigate how the effect of 24-hour restraint influences the outcome. Investigation of whether the type of removable restraint has an impact on the effectiveness of CIMT is also recommended. To a certain extent, a mitt or a glove allows the use of the well-functioning limb, whereas a sling excludes the use of this limb, possibly leading to greater use of the involved hand. It is also recommended that the compliance of the child and family with different types of restraints be investigated.[41] Gaining this perspective is important in understanding a family's view of balancing the burden of CIMT and the treatment effect. In the absence of current evidence for a superior effect of any particular type of restraint, the consensus group recommends that factors such as safety, comfort, climate, fabrics, and hygiene should be considered when selecting a restraint.

Does amount of training matter?

Literature. A fundamental principle of CIMT is the provision of intensive training to the affected hand.[30] Intensity or dosage of CIMT, however, is not easily defined. To describe and compare different models of CIMT, hours of structured training and programme length have typically been reported as a single unit of intensity (hours), either consistent or not consistent with hours of wearing the restraint. This method, however, fails to consider the interaction between the duration, frequency and length of the structured training programme. In this article, we discuss the amount of training based on (1) duration, the time (hours) of a single training session; (2) frequency, how often during the programme period the training is provided and; (3) length, the numbers of weeks for which the programme is provided (for further definition see Page et al.[42]).

The duration of structured training varies greatly across studies, from 1 to 6 hours of daily training,[18,27] whilst models of forced use provide no structured training.[15,43] To date, the effect of the amount of structured training has rarely been investigated. Gordon et al.[36] reported that 6 hours per day resulted in better outcomes than 2 hours per day using the same programme length and frequency. These results contrast with those of Case-Smith et al.,[18] who found no difference between groups which received 3 or 6 hours per day of training. Both research groups compared the same programme length and frequency, but children in the study by Case-Smith et al. used a non-removable cast, thereby undertaking additional unstructured training (i.e. forced use). Therefore, the specific impact of the amount of structured training may have been overshadowed by the continuous restraint.

The frequency of daily training across studies is commonly five to seven times a week; however, it is sometimes three times a week.[12,21] Across a range of environments, the reported training includes therapy-guided sessions[12] or supervised training from parents, teachers, students, or caregivers,[11,13] or a mixture of both.[26]

The length of CIMT programmes varies widely from 2 to 10 weeks. Group-based models of 2 to 3 weeks (training about 6h/d) have commonly been used for children from 4 years of age and older.[7,19,22,29] For younger children (<4y), models using 2 to 3 hours' training per day for 6 to 8 weeks have been more commonly used.[11,17,23,26] The difference in effect between short training durations over longer periods and high training durations over shorter periods has not yet been investigated.

It is important to recognize that, across studies, the duration and frequency of training is often not consistent with the targets specified in each model. For example, when the training is undertaken in a home or school environment, training has been reported to be 40% to 50% below the target hours.[11,13,23,26] Even in structured environments such as camps, the duration of active training achieved has been reported to be only 58%[7] or 81%[13] of the target duration.

Consensus for further research. Owing to the multivariable nature of dosage, the extent to which structured training influences CIMT outcomes remains unclear. Additional studies are required to identify the potential existence of a threshold effect for the amount of structured training. To investigate the effect of specific aspects of dosage, the duration of structured training, frequency of training, and programme length need to be independently varied within the same model of CIMT. This can be investigated by varying the hours of structured training between groups (e.g. 30h vs 60h) while maintaining the same programme frequency and length and type of restraint.[18] Equally, the distribution of training needs to be investigated by varying programme length whilst keeping the same duration and frequency of structured training and the same type of restraint (e.g. a total of 60h of daily training over 2 or 8wks).

Does the type of structured training matter?

Literature. The type of training varies significantly across models of CIMT, with all resulting in positive outcomes. The signature model of CIMT strictly includes shaping and repetition. Timers and logs are used to carefully monitor the temporal aspects of task performance.[44] In modified models of CIMT, principles of motor learning are more commonly used.[11–13,26] Training can be organized using activities chosen for training specific movements or hand skills or training can be focused more on the child's/adolescent's preference for play or activities that are then adapted to ensure success. To date, no study has directly compared the effect of different training concepts.

Consensus for further research. It is recommended that training concepts should be investigated by using a consistent duration, frequency, and length of training, but variation should be included in the training model. For comparison across models and translation into clinical practice, a precise description of the training needs to be documented. It is likely that the future development of CIMT will see innovation in the training methods (e.g. virtual reality and computer games)[45] and continued integration of bimanual training in conjunction with, or immediately after, CIMT (i.e. hybrid models).[10,12,18]

Does the environment and context of the training matter?

Literature. Efforts to adapt models of CIMT to become child and family friendly have resulted in considerable variation in the location and context in which training is provided. Group-based training programmes – embedded in circus groups, pirate groups and recreational/camp environments – have been popular, and these techniques have the aim of improving engagement and motivation.[12,19,22,46] There have also been individual-based models using the child's daily environment (home, day care, school).[11,23,26] The impact of the environment has rarely been investigated, with one small study that compared the impact of a home-based and clinic-based CIMT finding that outcomes favoured the home programme.[21]

Consensus for further research. Variation in the environment and the location between CIMT models appears to be based on age as well as practical, financial, and ideological reasons. Further investigation of how different environments influence treatment efficacy, compliance, and motivation for CIMT is recommended.

Does the provider of structured training matter?

Literature. The qualifications and number of providers for structured training vary across studies and include occupational therapists, physiotherapists, other professionals, interventionists (specially trained but not qualified), students, or parents. Who provides structured training is an important issue for implementation of CIMT into clinical practice owing to resource implications. Studies with large effect sizes support the premise that, after education and supervision, parents/teachers can be effective providers of CIMT.[11,13] No difference in outcomes was identified when comparing CIMT provided by qualified therapists or interventionists.[19,36]

Consensus for future research. The numbers of therapists/interventionists responsible for each child, for example a ratio of 1:1 or 3:1 (i.e. keeping children active with individualized attention), may influence the effects of training and is recommended for further investigation.

Optimal candidates for CIMT

Does age influence outcome?

Literature. The mean age of children across studies ranged from 2 to 7 years; however, studies have also included children as young as 7 months[6] while others have included adolescents.[22] In the only direct investigation of the effect of age, Gordon et al.[32] found no difference between outcomes in children aged 4 to 8 years compared with those aged 9 to 13 years. In other studies, a correlation of outcomes with age suggests inconsistent results, most likely owing to a small variation in age and a large variation in individual response to CIMT.[11,13,22,26] When comparing the results from a study including the youngest children (mean age 29mo) with a study including the oldest (mean age 10y 2mo), the effects measured using the AHA are somewhat better for the younger age group.[11,22] Based on the knowledge derived from the group data across studies, it is only possible to conclude that children of all ages benefit from CIMT. Theoretically, enhanced neuroplasticity of the young brain supports the assertion that 'the younger the better' for initiating CIMT.[47] It is also known that the highest rate of development of the affected hand in bimanual activities occurs before 3 years of age in more capable children, although it appears to plateau at 7 years of age.[48] This raises the possibility of a greater training effect in periods where rapid development commonly occurs.[26,35] However, from a practical perspective, older children may be more able to engage in highly intensive CIMT programmes and, contextually, group dynamics and teamwork may assist in their motivation and willingness to participate.[41]

Consensus for further research. The response to CIMT for children of different ages requires further investigation. Large studies including children across a broad age range would therefore be preferable. As this may not be possible, studies with distinct age groups could be used to compare age response with the same models of CIMT,[32] for example, 2 to 3 years, 7 to 8 years, and 15 to 18 years of age. The clear gap between age groups may clarify the effect of age on response to CIMT.

Does severity of impairment influence outcomes?

Literature. Studies of CIMT have generally included participants with moderately impaired hand function. Consistent with this, inclusion criteria have commonly adopted similar guidelines to studies of adults following stroke, including the ability to actively extend the wrist to 20°. This is a criterion now validated as the primary predictor of a successful response to CIMT in adults.[49] However, no such criterion has yet been identified for children with unilateral CP. Although several RCTs/CCTs including children with all levels of impairment have demonstrated positive outcomes following CIMT, the impact of severity on response to treatment remains unclear.[11,13,50]

Consensus for further research. Further research is needed to explore the primary predictors of positive change in order to identify the optimal group of children who respond positively to CIMT. Owing to limitations in task performance, participation in highly intensive CIMT programmes may be challenging for children with severe motor impairment. Similarly, the ability of children with cognitive impairment to maintain attention, follow instructions, and engage in

some models of CIMT may limit participation. For more severely involved children, modified, less intense models have shown positive outcomes.[12,13] Existing models of CIMT may need further adaptation to include the participation of severely impaired children.

Do lesion characteristics and corticospinal projections influence outcome?

Literature. There is evidence that the development of hand function is influenced by the type of brain lesion; however, the impact on outcomes following CIMT is unknown.[51,52] Different motor projection patterns are also known to influence the rate of development of hand function with a correlation between preserved contralateral motor projection patterns and good hand function.[51] It is plausible that the organization of corticomotor projections, as well as the type of brain lesion, might influence the response to CIMT. Kuhnke et al.[53] suggest that an increase in the speed of performance after CIMT seems to be related to the presence of contralateral corticomotor projections. However, more recent studies have shown that children, irrespective of motor projection patterns, can improve both the speed and the quality of movement (Islam ML, Nordstrand L, Holmstrom L, Kits A, Forssberg H, and Eliasson A, unpublished data).

Consensus suggestion for further research. Brain imaging and neurophysiological techniques are recommended to be used in future studies of CIMT to further explain the neurophysiological and structural prerequisites for effective treatment. These studies will also assist in defining the impact of neurological factors on the response to CIMT.

Prioritization of the defined questions

Of the 11 important questions identified, some were considered a higher priority by the group of experts to address in future research (Fig. 1). No question scored below a 3 on the 1- to 5-point scale of importance, indicating all were considered important. Three questions were identified as extremely important and require priority for further investigation: the influence of age on treatment effect (question 9); the effect of repeated CIMT (question 2); and whether the amount of training matters (question 5). The concept of intensive bursts of training across childhood seems promising. However, the interaction between programme length, duration, and frequency remains unclear. Focused studies targeting these variables using two experimental groups rather than a control group are now required. The consensus group recommends that future research prioritize these specific research questions in future studies.

It was recognized by further discussion that the type of restraint (question 8) is of high relevance for clinical implementation and requires further investigation. The question is whether non-removable restraints (i.e. casting) is more effective than periodic constraint. Likewise, comparison between forced use (i.e. casting and no training) and CIMT is important. The type of restraint used, in particular casting or removable devices, has raised mixed feelings among both clinicians and researchers owing to the perceived differences in efficacy, ethical concerns, and issues around compliance and child friendliness. Until potential differences in the effect of casting versus periodic restraint are known, it will not be possible to address these important issues.

Finally, important aspects of cost-effectiveness include who provides CIMT and in which environment CIMT is implemented. Existing models require different amounts of therapy-guided treatment, leading to vastly different costs. Some models require only a few hours of therapy-guided sessions while others have reported up to 126 hours of therapy-guided sessions. CIMT can take place in the child's daily environment, or in special recreational areas or hospitals, which has a further impact on cost. Forced use remains the cheapest model since it does not require any therapy-guided sessions, any specific location, or any materials. In future research, the interaction between cost and effect needs to be considered in addition to compliance and families' preferences.

Methods for evaluating effectiveness

Measuring outcomes

In the 23 RCTs, as many as 48 different clinical outcome measures were used, the majority being used by only one study. Table II lists the 17 tests that have been used in more than one study. This huge inconsistency prevents the pooling of data and precludes making objective conclusions about the effectiveness of CIMT. Other problems involve the use of measures without demonstrated validity, reliability, or sensitivity to change for the targeted group of children with unilateral CP. Furthermore, if the administration or scoring of a standardized measure has been adapted, the validity and reliability of the outcome is not maintained and therefore integrity of the measure is threatened.[54]

The most commonly used assessments (see Table II) can be categorized into (1) measures of body function/structure (grip strength, muscle tone and spasticity [the Modified Tardieu Scale and the modified Ashworth Scale (MAS)], and range of motion);[55,56] (2) unimanual measures of speed and dexterity (Bruininks–Oseretsky Test of Motor Proficiency,[57] Jebsen–Taylor Test of Hand Function[58]); (3) unimanual measures of quality of movement/skills (Quality of Upper Extremity Skills Test [QUEST], Melbourne Assessment);[59,60] (4) effectiveness of the use of the assisting hand in bimanual performance (AHA);[61] (5) parental questionnaire of the amount and quality of use of the affected arm (Paediatric Motor Activity Log [PMAL]);[6] and (6) individualized measures of functional performance (Goal Attainment Scaling and the Canadian Occupational Performance Measure).[62,63] Almost all studies report significant improvements following CIMT with the measures used. The exception concerns measures of body function (e.g. tactile sensibility,[7,22] range of motion,[12,27] and muscle tone.[7,23] Muscle tone and spasticity were generally only shown to change after CIMT when combined with anti-spasticity medication such as botulinum toxin-A.[14,26]

It was also observed that the frequent use of an outcome measure was not synonymous with scale validity and/or reliability.[64]

Consensus for future research. In order to contribute new knowledge, we recommend future studies use measures that allow the comparison of data across studies and which prioritize outcomes directly targeted by CIMT intervention. The choice of measure should be carefully matched to expected effects of the CIMT. Both unimanual capacity and bimanual performance need to be evaluated as primary outcomes since the CIMT training is focused on unimanual skills but the ultimate goal is to improve functional performance, typically requiring the use of both hands together. Unimanual object manipulation can be manifested by improved dexterity and speed of performance. In addition, quality of movements may improve after CIMT. Assessments evaluating child or parent self-reported opinions are important contributions, bringing knowledge about the individual's own perception and experience. Individualized outcome measures like Goal Attainment Scaling often show positive results. However, it is often not possible to practise activity-related goals, commonly requiring the use of two hands, within a unimanual CIMT programme; therefore, such goal achievement may not be the result of the CIMT per se.

Strengths and limitations of commonly used tests

Commonly used tests (Table II) assessing different aspects of hand function are described in detail in this section.

The Assisting Hand Assessment measures the bimanual aspects of hand function in children with a unilateral impairment: how effectively the affected hand is spontaneously used collaboratively with the well-functioning hand to perform bimanual tasks. Thus, the AHA measures important aspects that CIMT aims to improve and possesses strong psychometric properties, demonstrated in several studies.[61,65] Availability of the AHA is, however, limited by the need for a training course. Previous AHA results are inconsistently reported across studies using different types of scores. The interval-level logit, based on a 0 to 100 AHA-unit scale, is now recommended for reporting outcomes.[66]

The Paediatric Motor Activity Log is a parental report of how often and how well a child uses the more affected upper extremity after CIMT in (mostly) unimanual tasks.[6] The limitations are that the rationale and validity of the scale, the underlying theoretical construct, and how item selection was performed are not known.[67] Moreover, some items in the scale do not appear to be relevant to children across the age span used (7mo–8y of age). In different CIMT studies, both the original or modified/revised versions of the PMAL have been used without description of the reason or nature of the modification.[64] This makes interpretation of the results and comparison of the data across studies difficult.

The Jebsen–Taylor Test of Hand Function is a unimanual capacity measure of speed and dexterity.[57] This is important for the hand function aspect, and the test is frequently used in clinical trials with children with unilateral CP. However, additional psychometric data are needed for this population.[68,69] Information about test–retest reliability is still lacking, which is important for speed-related tests for children of different ages and with fluctuating muscle tone.

The Quality of Upper Extremity Skills Test measures the quality of movement, aiming to capture changes in grasp patterns, occurring before 18 months of age, and qualities of movements addressed in Neurodevelopmental Therapy (NDT)/Bobath treatment, for example, (1) dissociated movements; (2) protective extension; and (3) weight bearing.[59] Whether these aspects of hand/arm use are expected to change after CIMT should be considered. Psychometrics for the QUEST are established for the total scores involving both hands. Only the subscales for grasp and dissociated movements are commonly used in CIMT studies, and frequently for the affected hand only. These departures from standardized administration and scoring may invalidate outcomes of the QUEST. In a recent study using specially trained therapists, interrater reliability levels for the different domains were acceptable for group comparisons, except for the commonly used grasp domain.[70] The low reliability for this domain is possibly a result of scoring categories adopting typically developing grasp patterns, whereas grasp patterns in children with CP often look and develop differently.[70]

The Melbourne Assessment of Unilateral Upper Limb Function rates quality of movement in a single upper limb.[60] The items are scored on range, accuracy, dexterity, and fluency of movements. Two-thirds of the items making up the sum score are related to reaching and arm movements, with the rest related to grasp/release. The relatively low number of grasp and release items might reduce sensitivity to change after CIMT.

The MAS is used to grade muscle tone.[55] CIMT has, in general, not been shown to affect muscle tone. Furthermore, the reliability of the MAS has not been evaluated for upper limbs in children with CP. However, Klingels et al.[68] found test–retest reliability acceptable for group level comparisons for composite scores of the individual muscle groups and for individual muscles of elbow and wrist flexors. For all other individual muscles, test–retest reliability was lower. Thus, the consensus group does not recommended MAS for the evaluation of CIMT.

Reporting the effect of treatment

It is important to be able to compare the effect of the treatment between different studies. Commonly, authors report and interpret effect size estimates using Cohen's d.[71,72] However, depending on the statistical method used, effect size can also be reported using Pearson's r, the coefficient of determination (r^2), eta squared (η^2), or omega squared (ω^2).[73] In general, the larger the difference and the smaller the variability between groups, the larger the effect size. Therefore, for between-group estimations of effect, the type of control/comparison group significantly affects

the comparison between studies. For example, CIMT compared with a no treatment/usual-care control group is expected to result in a larger Cohen's *d* estimate than CIMT compared with a control group receiving a treatment of equal intensity (e.g. hand–arm bimanual intensive therapy). Additionally, if there is high variability in the response to treatment (perhaps owing to a broad spectrum of inclusion criteria), the estimates of effect are likely to be smaller owing to greater variability.

Treatment effect can also be evaluated in relation to the smallest detectable difference (SDD) for the outcome measure used. The smaller the SDD, the more sensitive the outcome measure is to change. At an individual level, a change on an outcome measure has to be equal to, or bigger than, the SDD level to be considered a real change.[66] Information about the SDD is available for only some measures. For the AHA, on the logit-based, 0 to 100 AHA-unit, scale an SDD is 5 units. For the QUEST, the SDD is reported to be 13.8% for the hemiplegic hand[74] and for the Melbourne Assessment the SDD was found to be 8.9%.[74] It is important to emphasize that the SDD is a quantification of random variation, inherent in all measures, and should not be confused with a clinically significant/important change. This latter is more complicated and is likely to be different for persons at different ends of the ability scale.

Consensus for future research. Future studies of CIMT should report the SDD and the proportion of children who achieve change greater than this amount, especially concerning the primary outcome measure, when available. We also encourage the calculation and reporting of the effect size and confidence intervals. The use of specific effect size estimates must be reported in the context of the analysis conducted.

CONCLUSION

The introduction of CIMT for children with unilateral CP has led to significant advances in the knowledge of upper limb intervention; it has clearly shown manual ability improves after training. Across all studies of CIMT, there are consistent positive findings. Through this consensus process, we have defined key ingredients and variables for CIMT that differ between studies. Based on the knowledge gaps in the literature and using the EUnetHTA framework, 11 questions of importance were identified and prioritized with the aim of guiding future research for CIMT. Further research should be highly prioritized towards (1) the effect of age on the treatment effect; (2) the effect of repeated CIMT; and (3) whether the amount of structured training matters. It should be highlighted that all existing models of CIMT can be used to further investigate these recommended questions, since all models are found to be effective. When using an existing model to further explore a question, it is important to ensure that only one of the variables is changed. A multitude of variables interacting within, and between, models creates significant confusion about what specific factors contribute to improvement.

Although not included in the prioritization process, methodological issues are essential for consideration in future research. It is important to select appropriate outcome measures. Measures should be related to the nature and goals of CIMT and, importantly, they should also be known to be reliable, valid, and responsive to change in children with CP. For the comparison of outcomes between studies, the consensus group also recommends the use of valid tools that have been used as primary outcomes in previous studies along with the addition of new valid and reliable measures as they are introduced.

No international guidelines exist for the implementation of CIMT into clinical practice, and very little is known about what the effect of treatment means in a child's life. What happens when CIMT is applied by a range of clinicians with different experience and education and in a more heterogeneous sample of children in clinical practice remains unknown. Whilst we recognize the importance of scientific freedom, we hope that the outcome of our consensus will result in more planned and systematic exploration of unanswered questions relating to CIMT.

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